Amendments to the Specification:

Please replace paragraph [009] with the following amended paragraph:

[009] FIG. 1: Western Blot analysis of efficacy of filtration of Ross River Virus harvest on removal of cellular proteins derived from cell culture. A: Detection of VERO cell protein with anti-VERO protein antibodies and B: Detection of Ross River Virus antigen with anti-RRV antibodies. It is shown is in lane 1: ~~Vero~~ VERO cell lysate as control, lane 2: RRV harvest after centrifugation, lane 3: after filtration, lane 4: after ~~Benzonase~~ BENZONASE endonuclease treatment, lane 5: after sucrose gradient purification.

Please replace paragraph [021] with the following amended paragraph:

[021] The cells can be bound to microcarrier during cell culture growth. The microcarrier can be a microcarrier selected from the group of microcarriers based on dextran, collagen, plastic, gelatine and cellulose and others as described in Butler (1988. In: Spier & Griffiths, Animal cell Biotechnology 3:283-303). Therefore, according to one embodiment of the invention the serum free or serum and protein free cells are cultivated and infected on microcarriers. Preferably, the microcarrier ~~are~~ is selected from the group of smooth surface microcarriers such as ~~Cytodex I®, Cytodex II® and Cytodex III®, Cytopore® or Cytoline® (all Pharmacia)~~ CYTODEX I microcarrier, CYTODEX II microcarrier and CYTODEX III microcarrier, and CYTOPORE microcarrier or CYTOLINE microcarrier (all Pharmacia).

Please replace paragraph [029] with the following amended paragraph:

[029] The filter used can be based a cellulose fiber matrix, hydrophilic filters, such as based on polyvinylidene fluoride membrane, or filters based on polypropylene membrane. Such filters are commercial available, ~~e.g. ZetaPlus® (CUNO), Durapore®, Millipak® or Millidisk™ (Millipore) or filters from Pall~~ e.g., ZETAPLUS filters (CUNO), DURAPORE filters, MILLIPAK filters or MILLIDISK filters (Millipore), or filters from Pall.

Please replace paragraph [033] with the following amended paragraph:

[033] The nucleic acid degrading agent according to the invention can be an enzyme which degrades nucleic acid, preferably a nucleic acid degradation enzyme, such as a nuclease, having DNase and RNase activity, or an endonuclease, such as from Serratia marcescens, commercial available as ~~Benzonase®~~ BENZONASE endonuclease (Benzon Pharma A/S). Most preferably the nucleic acid degradation agent is ~~Benzonase®~~ BENZONASE endonuclease.

Please replace paragraph [041] with the following amended paragraph:

[041] In accordance with another aspect of the invention, there is provided a vaccine against Ross River Virus infection comprising a host protective amount of Ross River Virus antigen in an amount of between 0.1 to 50 μg antigen / dose, preferably between [[0,3]] 0.3 and 30 μg antigen / dose. The antigen can be a whole virus or a fragment of the virus, such as a peptide or polypeptide, having an immunogenic epitope to induce protective antibodies against RRV infection. In a preferred embodiment of the invention the vaccine comprises as RVV antigen as whole inactivated virus.

Please replace paragraph [048] with the following amended paragraph:

[048] VERO cells (African Green Monkey, Cercopthecus aethiops, kidney) are used as a production cell line. The cells are been obtained from the American Type Cell Culture Collection, Rockville, Maryland at a passage number 124 under the designation ATCC CCL 81. The cells are adapted to grow in serum or protein free medium as described in Kistner et al., 1998 (supra) or WO 96/15231. For growth in serum free medium a basal DMEM HAM's F12 medium supplemented with inorganic salts, amino acids, sodium bicarbonate and yeast extract is used. The working cell bank is prepared without the use of any animal derived medium components. Cells of the working cell bank are expanded in T-flasks and roller bottles with a split ration of 1:6. Further propagation of the cells is performed in a stirred tank bioreactor using ~~Cytodex®~~ CYTODEX microcarrier as attachment substrate. The cells are grown at 37°C. The culture conditions of oxygen saturation 20%+/- 10% and pH7.25 +/-0.35 are kept constant during virus propagation process. A serum free cell culture system of VERO cells as described by

Kistner et al., (Vaccine 16:960-968 (1998) is infected with Ross River Virus at a multiplicity of infection (m.o.i.) of 0.001. After an incubation time of 3 days at 37°C the fermenter is harvested and virus is recovered from the cell culture supernatant. The harvested virus gave a titer of 8.0 $TCID_{50}$/ml after removal of microcarriers and cell debris by centrifugation (about 9000 g).

b) Purification of RRV

Please replace paragraph [049] with the following amended paragraph:

[049] The harvested virus is purified by filtering on a combination of a 1.2 µm filter (~~ZetaPlus®~~ ZETAPLUS filter, CUNO) and a 0.22 µm filter (~~Durapore®~~ DURAPORE filter, Millipore). The efficacy of the filtering to remove soluble proteins derived from the cell culture, in particular from VERO cells, is determined by Western blot analysis with VERO cell protein specific antibodies (Fig. 1 A). Fig. 1 impressively shows that the filtering removes substantially all VERO cell derived proteins from the virus preparation.

Please replace paragraph [052] with the following amended paragraph:

[052] After the filtering, ~~Benzonase®~~ BENZONASE endonuclease (2000 U/l) is added to the virus harvest to digest residual VERO cell and viral nucleic acid. During the following ~~Benzonase~~ BENZONASE endonuclease treatment the residual contaminants are removed with by a factor of at least 2.

Table 1

Determination of Virus titer and contaminating nucleic acid during Ross River Virus antigen purification process

Purification step	Virustiter ($TCID_{50}$ / ml)	Total Protein amount (µg / ml)	Vero cell DNA (pg / ml)	DNA / Protein (pg / µg)
Harvest	~~8,0~~ 8.0	86	54×10^4	6.300

Separator	~~7,6~~ 7.6	81	34×10^4	4.200
Filtration **1,2 µm / 0,2µm**	~~7,2~~ 7.2	80	14×10^3	175
Benzonase	~~7,4~~ 7.4	85	7×10^3	82
Sucrose gradient	inactivated	180	1×10^3	5.5

Please replace paragraph [053] with the following amended paragraph:

[053] After 1 h incubation at 37°C with ~~benzonase~~ BENZONASE endonuclease, formalin, as a virus inactivation agent with an end concentration of 0.1% (w/v), is added for total inactivation time of 120 h at 37°C. 24 hours after the addition of formalin, ~~Benzonase®~~ BENZONASE endonuclease (1000 U/l) is added again. Filtration steps on 0.22 µm sterile filter (Millipore) are performed at 0, 2, 6, 24, 48, 72, 96, 120, 144, 168 and 192 hours and samples for virus titration and safety experiments are drawn in parallel.

Please replace paragraph [055] with the following amended paragraph:

[055] The preparation comprising the inactivated virus is subjected to large scale flow zonal centrifugation over a 0-50% sucrose gradient to remove residual formalin, benzonase and nucleic acid break down products derived from the benzonase treatment. The sucrose gradient purification of inactivated virus resulted in one peak at sucrose concentration between 40% and 42%, demonstrating a pure and homogeneous antigen preparation. The fractions containing the virus are pooled and subjected to a [[0,2]] 0.2 µm sterile filtration step.

Please replace paragraph [058] with the following amended paragraph:

[058] Determination of the Effective Dose (ED_{50}) of antigen is performed by adjusting the RRV antigen concentration to 10 µg/dose, without and with $Al(OH)_3$ as an adjuvant at concentration of ~~0,05%, 0,1% and 0,2%~~ 0.05%, 0.1% and 0.2% (w / v). The candidate vaccine preparation is

then diluted in 4 fold steps. Each dilution is injected into a group of 10 CD1 mice. After 4 weeks, the mice are boostered with the respective amount of antigen. Blood samples are drawn at 4 weeks, before the booster, and at 6 weeks after the booster. The sera of the samples are analyzed by a RRV-antibody ELISA and the ED_{50} is calculated. Table 3 shows the ED_{50} of the vaccine with and without adjuvant. To induce an immune response with similar antibody titers, in the vaccine comprising an adjuvant only 1/5 to 1/20 of the amount of antigen of the vaccine with adjuvant is needed, depending on the adjuvant concentration used. The increasing the adjuvant concentration in the final preparation allows reduction of virus antigen amount in the vaccine. This is in contrast to prior art results of Yu et al. and Aaskov et al. (*supra*) , which had showed negative influence of adjuvant on protective antibody induction.

Table 3:

Effective Dose (ED_{50}) and Protective Dose (PD_{50}) of RRV Vaccine in mice

ED_{50} Antigen (ng) 4 weeks	**ED_{50} Antigen (ng) Booster 6 weeks**	**PD_{50} Antigen (ng) 6 weeks**	**Adjuvant $Al(OH)_3$**
413	150	1250	-
83	2	20	~~0,05%~~ 0.05%
74	9	20	~~0,1%~~ 0.1%
20	7	20	~~0,2%~~ 0.2%